# DRUGS IN THE TREATMENT OF ENDOMETRIOSIS

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## Introduction

Endometriosis affects approximately 3% of women of reproductive age. The term *endometriosis* is applied to a condition where actively functioning endometrium is found in ectopic situations other than lining the uterine cavity, such as bladder, ovaries, intestines. This tissue responds to monthly cyclical hormonal changes and has no means of escaping the body when it has broken down. While normal endometrium is expelled as menstrual bleeding, ectopic endometrial tissue remains in the body causing inflammation, pelvic pain, abnormal menstruation and infertility. If left untreated, the condition becomes worse.

Current evidence suggests that menstrual relfux into the pelvis and the secretion of oestrogen are central to the pathogenesis of endometriosis. Menstrual reflux could be affected by contraceptive use, decreasing parity, delay in attempting pregnancy, tubal occlusion and the use of tampons.

Conservative treatment involves the use of hormonal agents, including oestrogen-progesterone preparations and progesterone-only regimens for a pseudopregnancy effect, whilst GnRH agonsists and danazol induce a pseudopregnancy effect.

This study aims at investigating the incidence of endometriosis in Maltese women, what drugs are being used to treat this condition, and what are the main side-effects being experienced. All the above mentioned preparations for endometriosis are available at St. Luke's Hospital, with the exception of the GnRH-a.

## Methodology

### Survey 1

### Retrospective Study

a) The files of all women who underwent a laparoscopy at Karin Grech Theatre during 1990 were screened for any cases of endometriosis.

b) The number of patients to whom danazol was prescribed during the year 1990 was obtained from records at the Pharmacy Unit. These patients' files were also screened.

All files were obtained through the Gynae Outpatient's Department. The following information was retrieved:

i) the incidence of endometriosis in Maltese women
ii) the most common age group in which endometriosis occurred
iii) the most common symptoms associated with this disease
iv) the extent of disease
v) menstrual cycle patterns
vi) whether a correlation existed between endometriosis of a delay in attempting pregnancy
vii) what drugs were being used to treat the condition

Survey 2

**Patients receiving Danazol treatment**

Twenty patients treated with danazol for a duration of 3 - 6 months obtained their medication free of charge from the St. Luke's Hospital pharmacy on a monthly basis between July and December 1991. When the patients visited the hospital pharmacy to collect their medication, they were interviewed and the results compiled on a questionnaire format. The patients were mainly asked about their presenting complaint which led to the diagnosis of endometriosis and whether there were any experiences of adverse effects. The patients were also asked whether they were given any information about their condition and whether they were satisfied or felt the need to know more.

Survey 3

**Gynaecologists' views on the drugs used for Endometriosis**

Questionnaires were sent to twenty gynaecologists working at St. Luke's Hospital. It was attempted to investigate their views on the drug treatment of endometriosis, whether they are satisfied with the drugs available in hospital, or whether they would rather prescribe some alternative form of therapy.

## Results

### Survey 1

A total of 50 files were screened: 40 patients were recorded to have been prescribed danazol during 1990; 10 patients were diagnosed as having endometriosis by laparoscopy.

The modal age group in which endometriosis occurred was between 31 - 35 years (n=13), and up to 5 years before and after this age bracket [(n=12) and (n=11) respectively]. Only 1 patient over 50 years of age had endometriosis.

The majority of patients had their first period at 11 - 12 years of age (n=21). Equal numbers of patients (n=21) suffered mild and moderate losses, whilst pain was mild in 52% (n=26) of the patients. Menstruation tended to last for 5 - 7 days in the majority of patients (44%, n=22).

10% (n=5) of the women studied were single, eighteen patients had children and 8 of those who became pregnant experienced miscarriages. The modal age group at first pregnancy was between 26 - 30 years.

**Table 1:** Most common symptoms associated with Endometriosis

| Presenting complaint | Number of patients Total | 1st complaint | 2nd complaint |
|---|---|---|---|
| Infertility | 31 (62%) | 27 | 4 |
| Dysmenorrhoea | 9 (18%) | 4 | 5 |
| Pelvic pain | 15 (30%) | 12 | 3 |
| Dyspareumia | 8 (16%) | 1 | 7 |
| Nausea | 5 (10%) | -- | 5 |
| Spotting | 4 (8%) | 2 | 2 |
| Menorrhagia | 4 (8%) | 2 | 2 |
| Other* | 5 (10%) | 2 | 3 |

* include pain on micturition, recurrent abortions, ovulation pain

Approximately 52% (n=27) suffered from only one symptom whilst 46% (n=23) experienced more than one symptom. 40% (n=20) had moderate endometriosis, whilst 20% (n=6) had extensive endometriosis.

The most frequently used regimen for danazol was 200mg tds, 75% (n=32), for a total of 6 months, 73% (n=29). Adjunct therapy was used in two cases.

**Table 2:** Drugs employed in the treatment of Endometriosis

| | Danazol | Progestogens | Ovulatory | None |
|---|---|---|---|---|
| Number of Patients | 40 | 7 | 1 | 2 |

The most frequently used regimen for danazol was 200mg tds, 75% (n=32), for a total of 6 months, 73% (n=29). Adjunct therapy was used in two cases.

**Table 3:** Outcome of Danazol Therapy

| Effect | Number of Patients |
|---|---|
| Breakthro' bleeding | 12 |
| Changed $R_x$ | 1 |
| Increased dose | 4 |
| Decreased dose | 1 |
| $R_x$ stopped | 4 |
| Became pregnant | 3 |
| Delivered | 2 |

The dose of danazol had to be increased in 4 patients (8%) due to breakthrough bleeding which occurred in 24% (n=12). Four patients

stopped danazol $R_X$ before the stipulated date, one of which was found to be allergic to danazol.

**Survey 2**

Most of the twenty women interviewed with endometriosis were aged between 31 - 40 years (n=11), followed by 26 - 30 years (n=7).

Half of the patients had a 200mg tds regimen and the remainder 200mg qid. The duration of therapy was 6 months for 18 patients and 3 months for 2 patients. Nineteen patients were prescribed danazol for the first time, whilst one patient was taking danazol on a repeat prescription.

19 patients claimed to be experiencing side-effects, whilst one patient did not. 80% of patients experienced more than one side-effect. Half of the patients experienced breakthrough bleeding, which persisted in all the 6 cases where the dose was increased.

**Table 4:** Commonest side-effects experienced with Danazol

| Side-effect experienced | Number of patients |
|---|---|
| Hot flushes | 13 |
| Breakthrough bleeding | 11 |
| Back pain | 6 |
| Bloatedness | 6 |
| Weight gain | 4 |
| Acne | 2 |
| Hirsutism | 1 |

All patients were given information about endometriosis either by a consultant (80% [n=16]), or by someone else (20% [n=4]). Only one patient was given a leaflet in addition to verbal advice. 85% (n=17) of the women felt that they were satisfied with the information given, whilst 15% (n=3) felt the need to know more. Although most patients were informed about their condition, they claimed that they had no written literature to refer to, especially concerning the side-effects of their drug therapy. The drug was in fact dispensed from the pharmacy without any accompanying package information.

Survey 3

3 senior house officers, 4 consultants and 6 senior assistants responded, making up a 65% response (n=13) rate.

According to them, the most common primary symptoms associated with endometriosis are dysmenorrhoea (n=7), followed closely by infertility (n=6) and dyspareunia (n=1). The commonest age groups were between 26 - 30 years (n=7) and between 31 - 40 years (n=6).

Eight gynaecologists claimed that they use danazol as the first drug of choice. 2 of these said that they would use GnRH-a as a second-line drug. Progesterone-only regimens were favoured by 2 doctors, GnRH-a by one and another claimed to have no drug of choice.

Reasons for choosing danazol included the fact that it is less expensive than some forms of therapy, is quite effective especially for treating infertility and that it is relatively free from side-effects. Others use danazol because they have more experience with this drug. In the case of a few Senior House Officers or Senior Assistants, the drug was used because it was prescribed by the consultant. Only 5 out of 12 gynaecologists said that danazol gave rise to serious side-effects. All but one agreed that GnRH-a will be used in the future and only 2 disagreed that the expense would be justified. However, this would depend on whether the drug is available through hospital services. 5 gynaecologists stated that laser laparoscopy would supercede drug therapy.

Conclusion

The first survey concludes that endometriosis seems to affect 0.07% of the Maltese women population and are principally aged between 31 to 40 years. The incidence in Maltese women is much lower than the 1 - 5% incidence rate reported in other studies.

The most common symptoms associated with endometriosis was infertility at a rate higher than that estimated by some reports, whilst the percentage of women suffering from dysmenorrhoea was lower. The percentage of women experiencing dyspareumia and menstrual irregularities seemed to be within ranges estimated in some investigations.

The most popular drug used in treating endometriosis was danazol, but Survey 2 concluded that its use was related to a number of adverse effects, namely breakthrough bleeding and hot flushes. Although most adverse effects are unavoidable and often of minor importance, they will certainly affect the quality of the patients' lives, especially when more than one adverse effect is experienced.

In general, the gynaecologists' view on medical treatment with danazol (as concluded in the third survey), is speculative. It has a limited role, especially since it is difficult to optimise treatment with a limited choice of drugs. Some gynaecologists claim that medical treatment is ineffective for pain with little effect in improving fertility, preventing recurrence of endometriosis or long-term sequelae of the disease. One also has to balance long-term treatment and the delay in trying to conceive in patients suffering from infertility. Some suggest that only mild to moderate cases should be treated and these should be closely followed with repeat laparoscopies and monitoring of side-effects.

Only exceptionally few cases of endometriosis were given a classification of the extent of their disease. Some sort of survey sheet classifying the various stages of endometriosis should be introduced. A suggested format is that used by the American Fertility Society Revised Classification of Endometriosis.

Pharmacists can help by monitoring the patients' progress when they attend the pharmacy for repeat prescriptions. They should enforce any information given, especially on the issue of physical methods of contraception during danazol use, and making sure that they comply with the drug regimen. The latter may be difficult for some patients who do not feel that they know enough about the drugs that they are taking. Thus, as part of this dissertation, an attempt has been made to compile concise information about endometriosis and danazol in the form of a handy leaflet, and distributing these leaflets to danazol patients at the Out Patients' Dispensary at St. Luke's Hospital.

**References**

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